Occupational Cancer

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Bernardino Ramazzini
De Morbis Artificum, 1700

"Every city in Italy has several religious communities of nuns, and you can seldom find a convent that does not harbor this accursed pest, cancer, within its walls. Now why is it that the breasts suffer for the derangements of the womb, whereas other parts of the body [uterus] do not suffer in this way? Now, these are not caused by suppression of the menses but rather, in my opinion, by their celibate life."

Outline

1. How much cancer is due to occupation?
2. How might an occupational exposure cause cancer?
3. What occupational exposures cause cancer?
4. When might a cancer be occupational?
5. What can be done?

Cancer in the USA – 2008 estimates

- 1,437,180 new cases
- 565,650 deaths
- Second leading cause of death

(Source: Ries LAG, Melbert D, Krapcho M, Stinchcomb DG, Howlader N, Horner MJ, Mariotto A, Miller BA, Feuer EJ, Altekruse SF, Lewis DR, Clegg L, Eisner MP, Reichman M, Edwards BK (eds). *SEER Cancer Statistics Review, 1975-2005*, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2005/, based on November 2007 SEER data submission, posted to the SEER web site, 2008.

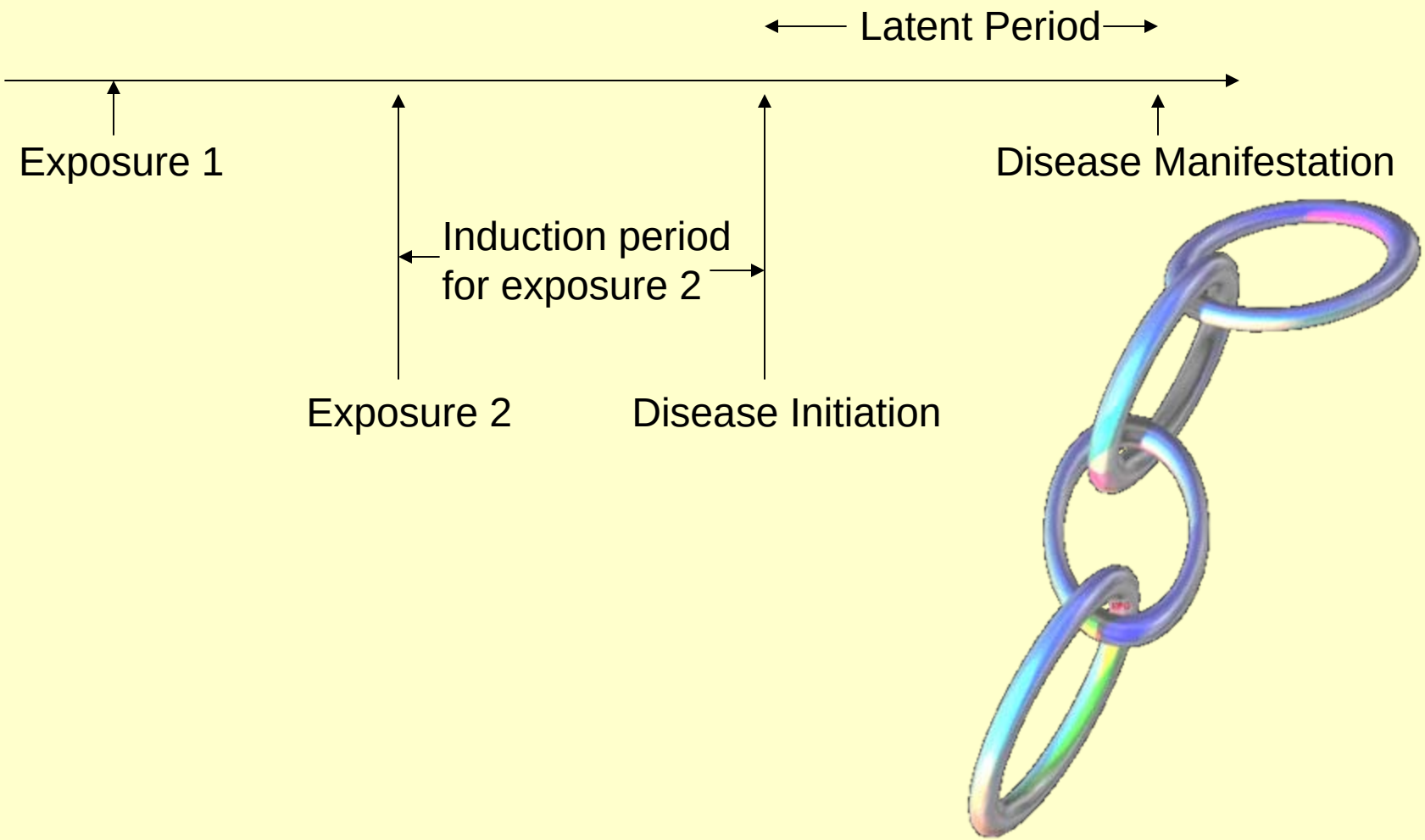
1. How much cancer is due to occupation?

30%	Tobacco
30%	Diet / Obesity / Physical inactivity
7%	**Occupation / Environment**
5%	Family history
5%	Biological agents
5%	Perinatal effects / Growth
3%	Alcohol
3%	Reproductive factors
2%	Radiation/sunlight
10%	Unknown
100%	

Source: Cancer Care Ontario website http://www.cancercare.on.ca/index_statisticsAllSites.htm#fn4 citing Adami et al., 2001 and Colditz et al., 1996. Causes of Cancer Deaths in Developed Countries.


How many causes are there for any one outcome?

A causal chain



2. How might an occupational exposure cause cancer?

Sources of information

- Animal and *in vitro* studies
- Human epidemiology, vast majority involve ionizing radiation exposure
  - Atomic bomb survivors in Japan
    - Life Span Study
    - http://www.rerf.or.jp/library/archives_e/lsstitle.html
  - Iatrogenic (mis)use
    - Examples: ankylosing spondylitis, *tinea capitis*, cancers

Carcinogenesis

- Fundamental event is alteration in DNA leading to unregulated cell growth – ‘single hit’
- Alteration must be stable and non-lethal
- Humans have ~ 30 000 genes
  - 50 – 100 oncogenes
  - Mammalian origin
- Specific genetic mutations associated with occupational cancers / exposures
  - tumor suppressor gene p53 and VCM

    (Smith SJ et al. *Molecular epidemiology of p53 protein mutations in workers exposed to vinyl chloride.* Am J Epidemiol. 1998 Feb 1;147(3):302-8).

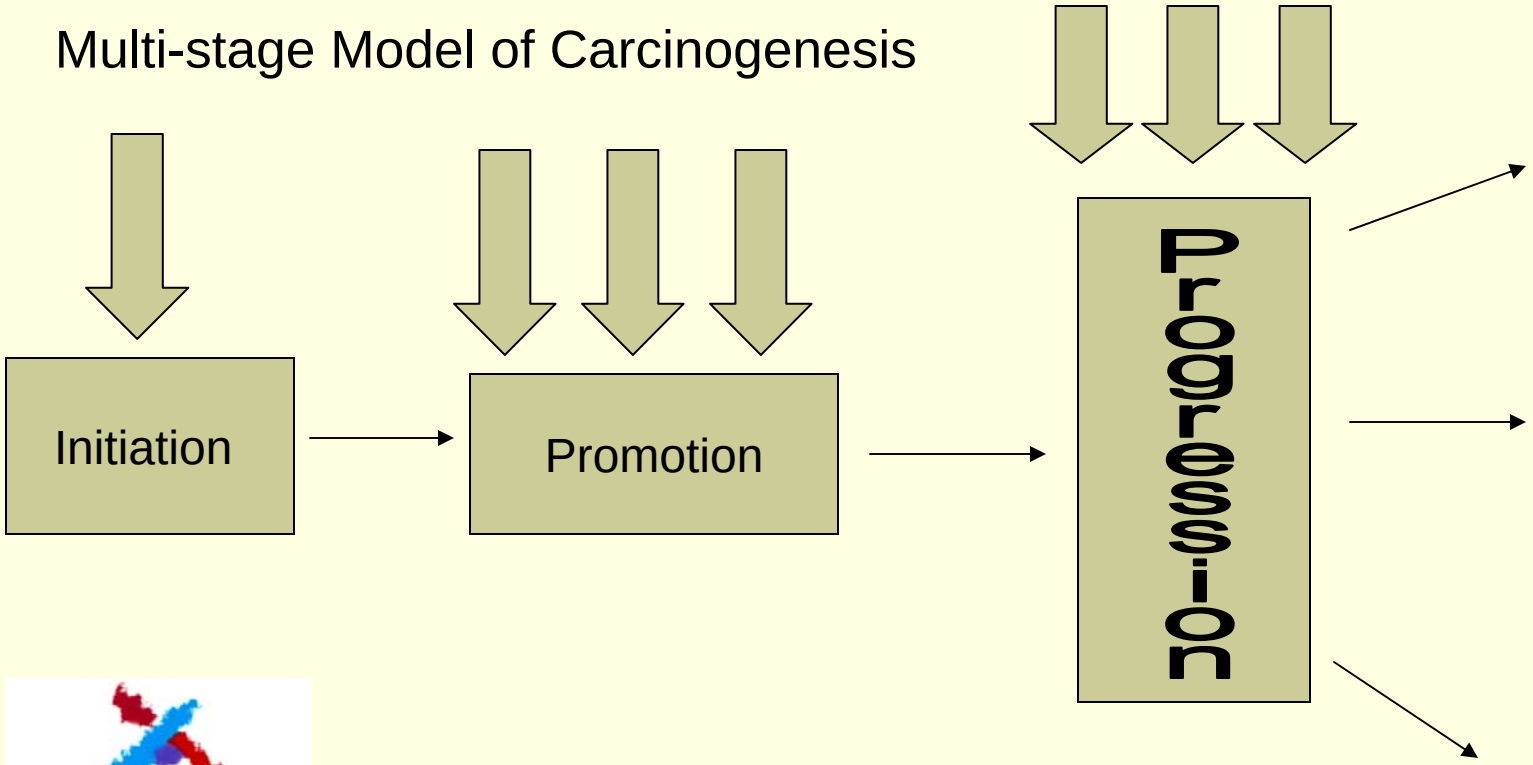
Mouse skin model

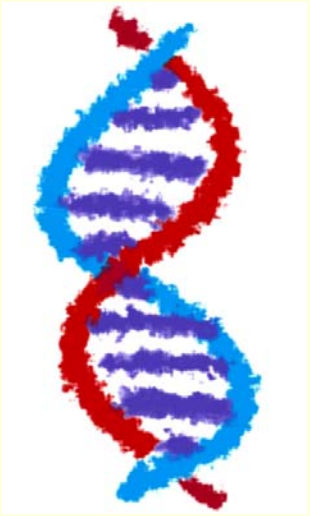
Carcinogenesis

Multi-stage model:

1. Initiation
2. Promotion
3. Progression

Multi-stage Model of Carcinogenesis





Initiator vs Promoter

- Carcinogen
- Damages DNA
- No apparent threshold
- Single hit

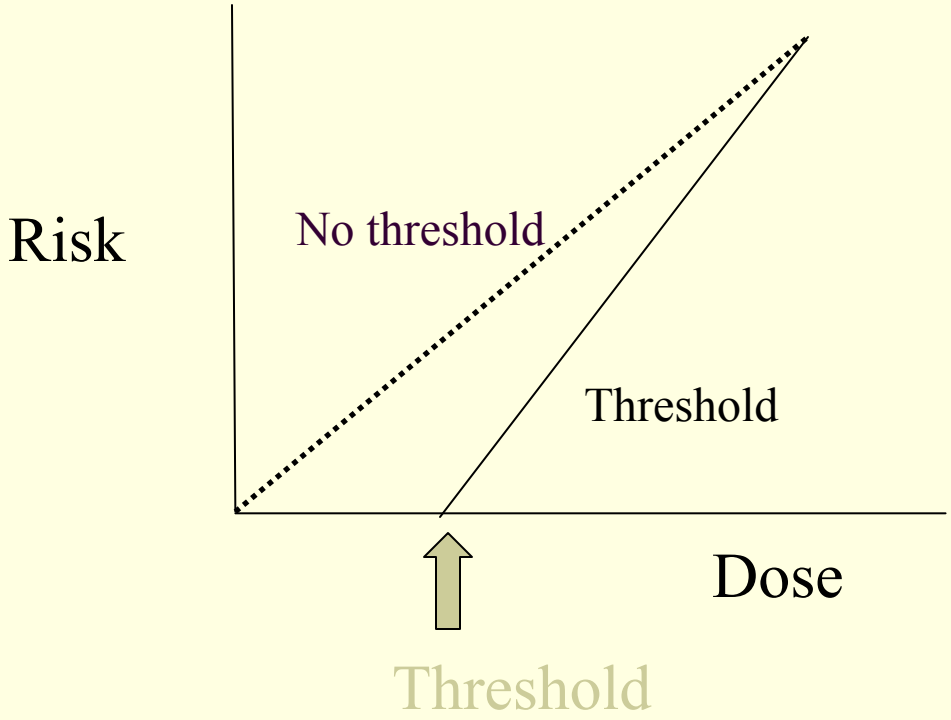
- Not carcinogenic, unless preceded by initiation
- Epigenetic
- Threshold
- Prolonged exposure needed

Types of carcinogens

- “Incomplete” carcinogen requires a promoter
  - Example: bis (chloro-methyl) ether
- “Complete” carcinogen both initiates and promotes
  - Example: cigarette smoke
- “Co-carcinogen” enhances genotoxic effect of initiator when given *at the same time*
  - Example: ethanol and VCM

No Threshold Model

No threshold model drives regulatory climate for carcinogens.



Regulating occupational carcinogens

- Exposure limits will include *safety or uncertainty factor*
  - Usually 100 or 1,000
  - Not based on science, but consensus
- Exposures to known carcinogens require:
  - Justification
  - Optimization
    - Application of “ALARA” principle
  - Limitation

(Source: International Commission on Radiological Protection at www.icrp.org)

3. What occupational exposures can cause cancer?

International Agency for Research on Cancer (IARC)

- Part of the World Health Organization (WHO)
- http://www.iarc.fr

International Agency for Research on Cancer (IARC)

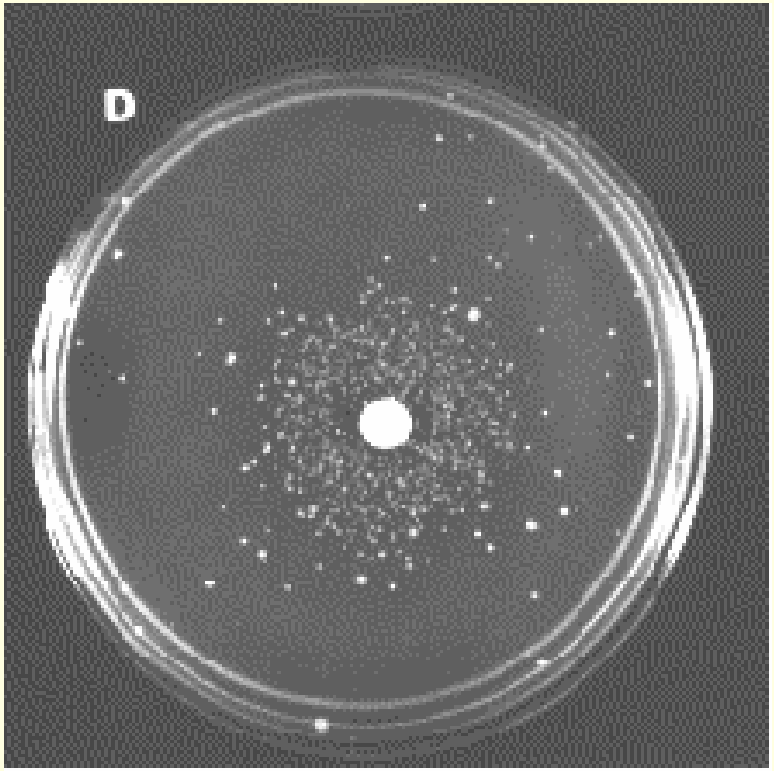
- Standardized evaluations of the strength of the evidence for carcinogenicity
- Evaluations of > 900 agents in 91 monographs (published as of June 2008)
  - ‘agent’ may be chemical, mixture, biological agent, industry, etc.
- Data summaries and evaluations available online

IARC Evaluation

- Review:
    1. laboratory experiments
    2. human epidemiology
- Grade evidence for each as *sufficient, limited* or *inadequate*
- Consider other data (pathology, genetics, structure-activity relationships etc.)
- Provide overall evaluation

1. Laboratory Experiments

- *In vivo* (animal) studies
  - For IARC, may be only species
- *In vitro* studies
  - Ames' test



IARC Overall Evaluation

	Evidence in humans	**Evidence in animals**
Group 1 The agent is carcinogenic to humans	Sufficient	Sufficient
Group 2A The agent is probably carcinogenic to humans.	Limited	Sufficient
Group 2B The agent is possibly carcinogenic to humans.	Limited	Limited
Group 3 The agent is not classifiable as to its carcinogenicity to humans.	Inadequate	Inadequate or limited
Group 4 The agent is probably not carcinogenic to humans.	Evidence for *lack* of carcinogenicity	Evidence for *lack* of carcinogenicity

IARC Overall Evaluation

- With 935 agents evaluated, which group is the largest?

1. Carcinogenic
2. A. Probably carcinogenic
   B. Possibly carcinogenic
3. Not classifiable
4. Probably NOT carcinogenic

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   B. Possibly carcinogenic
3. Not classifiable (515)
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IARC Overall Evaluation

- With 935 agents evaluated, which group is the smallest?

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2. A. Probably carcinogenic
   B. Possibly carcinogenic
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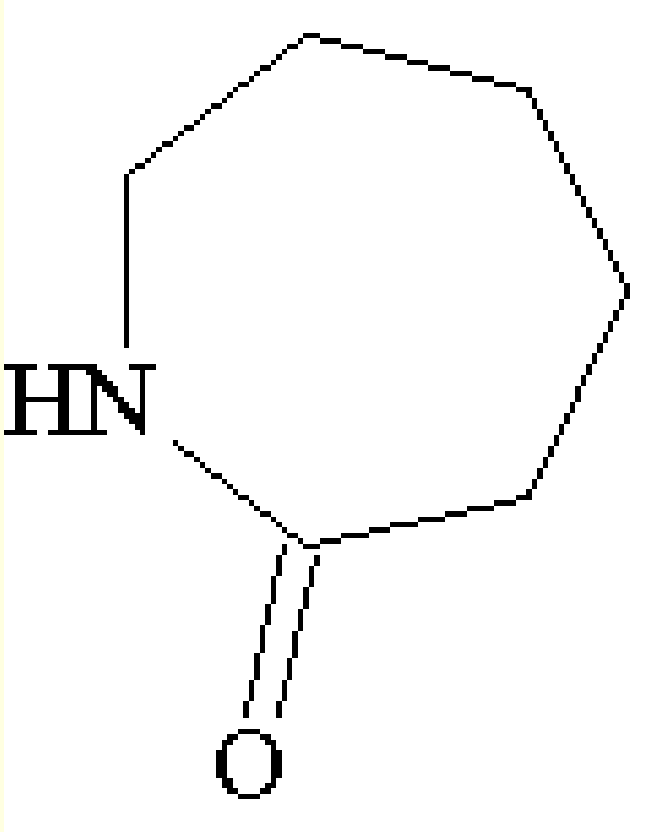
4. Probably NOT carcinogenic

Caprolactam

- Used in nylon fiber production



IARC Overall Evaluation (July 2008)

1. Carcinogenic (105)
2. A. Probably carcinogenic (66)
   B. Possibly carcinogenic (248)
3. Not classifiable (515)
4. Probably NOT carcinogenic (1)

Some IARC Group 1 Carcinogens

- Alcoholic beverages
- Arsenic
- Asbestos
- Benzene
- Benzidine
- Beryllium
- Bis-chloromethylether
- Chromium VI
- Coal tars
- Hepatitis B,C virus
- Nickel
- Polynuclear aromatic hydrocarbons (PAHs)
- Rubber industry
- Silica
- Sulfuric acid mist
- X and γ radiation
- Vinyl chloride
- Wood dust

IARC Evaluations

- Note: strength of evidence for any one agent may vary depending site, overall evaluation reflects strongest evidence.

Example: Asbestos is a Group 1 carcinogen, but evidence for lung cancer, mesothelioma is greater than for GI, laryngeal malignancies

- Evaluation says nothing about potency.
- Not without controversy.

National Toxicology Program (NTP)

- congressionally mandated to produce Report on Carcinogens (RoC)
- listed as either
  - "*known to be a human carcinogen*" or
  - "*reasonably anticipated to be a human carcinogen*"
- “Known” requires sufficient evidence in humans and both require evidence from more than one species of animal
- OSHA / California Proposition 65 both use either NTP designation as authoritative for carcinogens

4. When might a cancer be due to an occupational exposure?

Occupations with well-documented increased rates of cancers

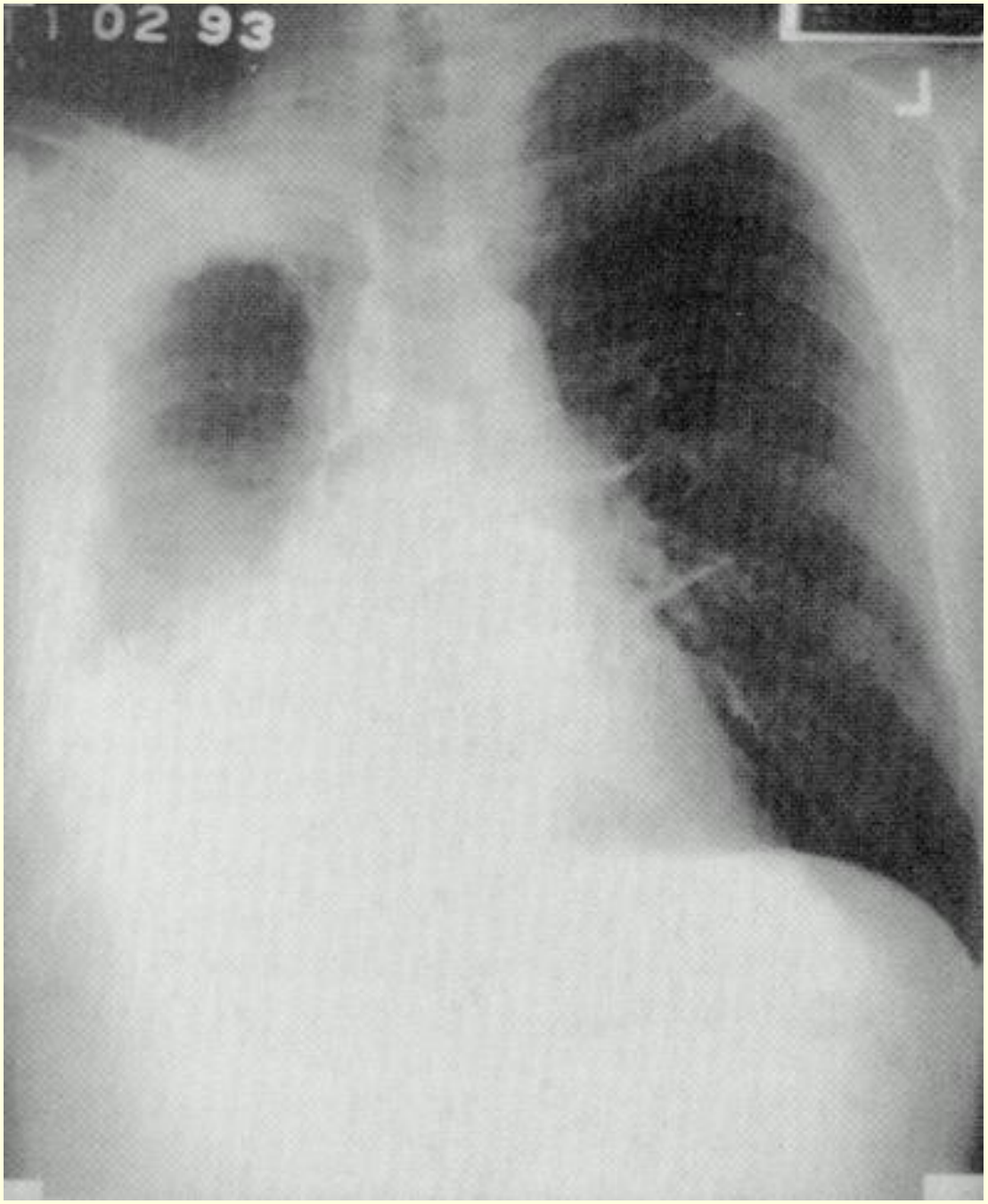
Occupation	Cancer	Agent
Dye manufacturers, rubber workers	Bladder	Aromatic amines (4-aminodiphenyl benzidine,2-naphthylamine)
Copper smelters	Lung	Arsenic
PVC manufacture	Liver (angiosarcoma)	Vinyl chloride monomer
Hardwood furniture and leather manufacture	Sinonasal	Wood and leather dust
Outdoor workers	Skin	UV light
Roofers, asphalters	Skin, scrotum, lung	Polycyclic hydrocarbons in soot, tar, oil
Asbestos mining & milling, insulation & shipyard workers	Lung, mesothelioma	Asbestos

Occupations with well-documented increased rates of cancers

Occupation	Cancer	Agent
Glue, solvent workers	Leukemia	Benzene
Nickel refining	Lung, nasal	Nickel (Soluble compounds)
Uranium and other miners	Lung	Radon (Ionizing radiation)
Chrome and pigment manufacture, chrome platers	Lung, sinonasal	Chrome (VI)
Cadmium alloying and processing	Lung	Cadmium
Plastic and ion-exchange resin manufacture	Lung (small cell)	Bis(chloromethyl)ether

When might a cancer be occupational?

1. When you see an unusual cancer.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Mesothelioma

- Malignancy of pleura, peritoneum tunica vaginalis, ovary
- Incurable, very poor prognosis (months)
- Increasing incidence (3000 per year in US)
- Associated with asbestos exposure in about 80% of cases
  - Recall: long latency
  - May follow seemingly trivial exposure
  - No association with smoking

Angiosarcoma of the Liver Among Polyvinyl Chloride Workers – Kentucky (MMWR 1974;23:49-50)

Case	Age at onset	Date of illness onset	Date of Diagnosis	Date of Death	Years employed
1	43	Aug 1967	Sept 1967	Jan 7, 1968	17
2	36	Jan 1970	May 1970	Sept 27, 1971	14
3	41	Jan 1964	Mar 1973	Mar 3, 1973	14
4	58	July 1973	Dec 1973	Dec 19, 1973	27

Angiosarcoma of the liver and vinyl chloride monomer

- 4 cases identified between September 1967 and December 1973
- All were employed in polyvinyl chloride polymerization section of a plant near Louisville, Kentucky employing 270 people
- General population rate at that time

  = 25 cases per year in US
- One of the classic case clusters in occupational medicine
- Associated with vinyl chloride monomer exposure
  - Highly reactive gas

Occupational cancers

- However, the vast majority of occupational cancers are the same as those observed in general population
  - Lung, leukemia, bladder

When might a cancer be occupational?

1. When you see an unusual cancer.
2. When you see an increased frequency of a cancer.

The first recognized occupational cancer (1775).

The most recently recognized occupational cancer?

- IARC, October, 2007: Shift-work that involves circadian disruption is probably carcinogenic to humans (Group 2a)
  - Limited evidence in humans, mostly cohort studies of nurses and female flight attendants showing modest increase in breast cancer
  - Sufficient evidence in animals
    - Increased tumors with circadian disruption
    - Increased tumors with removal pineal gland

Background ‘noise’

- Lifetime prevalence of being diagnosed with an invasive cancer (both genders)?

- Lifetime risk of dying from cancer?

Background ‘noise’

- Lifetime prevalence of being diagnosed with an invasive cancer?
  - 41%
- Lifetime risk of dying from cancer?
  - 21%

(Source: Ries LAG, Melbert D, Krapcho M, Mariotto A, Miller BA, Feuer EJ, Clegg L, Horner MJ, Howlader N, Eisner MP, Reichman M, Edwards BK (eds). SEER Cancer Statistics Review, 1975-2004, National Cancer Institute. Bethesda, MD, http://seer.cancer.gov/csr/1975_2004/, based on November 2006 SEER data submission, posted to the SEER web site, 2007.

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When might a cancer be occupational?

1. When you see an unusual cancer.
2. When you see an increased frequency of a cancer.
3. When you see a cancer earlier than expected.
4. When you see the right cancer ***at the right time*** following a compatible exposure.

leukemia: 5 - 10 years

mesothelioma: 40 - 50 years

When might a cancer be occupational?

1. When you see an unusual cancer.
2. When you see an increased frequency of a cancer.
3. When you see a cancer earlier than expected.
4. When you see the right cancer at the right time following a compatible exposure.
5. When you see other end organ effects of the carcinogenic exposure.

5. What can be done?

Prevention

- Specific measures (WHO, April 2007):
  - stop the use of asbestos
  - substitute benzene in organic solvents
  - use technologies that convert carcinogenic chromium into a non-carcinogenic form
  - ban tobacco use at the workplace
  - provide UV protection for outdoor workers

Source: http://www.who.int/mediacentre/news/notes/2007/np19/en/index.html

Summary

- Impossible to know what fraction of cancer is ‘occupational’
- ‘Single hit’ hypothesis means that regulation of carcinogens is more stringent
- Carcinogenesis is evaluated through animal and human epidemiological studies, each having important limitations
- Several factors may suggest that an occupational exposure is playing role in carcinogenesis
- Primary, rather than secondary, prevention is critical